Cont B1

a' cont

interferon-γ production, said adjunct therapeutic agent comprising a retinoid, interleukin-15, interleukin 18, interferon-α or interferon-γ.

REMARKS

Claims 1-3 are pending in the instant application. Claims 1-3 have been rejected. Claim 3 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of this amendment and the following remarks.

I. Rejection of Claim 3 under 35 U.S.C. § 102(b)

Claim 3 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Haku et al. 11/97. The Examiner suggests that Haku et al. disclose a composition comprising a recombinant interleukin-12 (IL-12) and recombinant interleukin-2 (IL-2) and show that the combination of IL-12 and IL-2 at a suboptimal or optimal concentration augmented IFN-γ production.

Applicant respectfully disagrees with the Examiner's characterization of the teachings of Haku et al.

Contrary to the Examiner's suggestion, Haku et al. does not teach that suboptimal and optimal concentrations of IL-2 augmented IFN-γ production. Instead, Haku et al. teach that IL-12 and a suboptimal dose of IL-2 had additive effects in inducing MNC killer

activity. In contrast, Haku et al. showed that an optimal dose of IL-2 with IL-12 suppressed killer induction.

However, in an earnest effort to advance the prosecution of this case, Applicant has amended claim 3 to clarify that the adjunct therapeutic agent comprises a retinoid, interleukin-15, interleukin 18, interferon-α or interferon-γ. Support for this amendment can be found in the specification at page 8, lines 14-17. Since Haku et al. does not teach compositions comprising these adjunct therapeutic agents, this reference cannot anticipate claim 3 as amended.

Withdrawal of this rejection is respectfully requested in light of the amendment to claim 3.

II. Rejection of Claim 1 and 3 under 35 U.S.C. § 103(a)

Claims 1 and 3 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Rook et al. (1996) in view of Haku et al. (November 1997). The Examiner acknowledges that neither Rook et al. nor Haku et al. teach a method for treatment of advanced cutaneous T cell lymphoma in a human by administering recombinant IL-12 (claim 1) and an adjunct therapeutic agent which stimulates IFN-γ production. However, the Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made, to design a method of treating

advance cutaneous T cell lymphoma in a human by administering recombinant IL-12, because Rook et al. teach that exogenous recombinant IL-12 enhanced depressed IFN-γ production by PBMCs from SzS patients and enhanced cell-mediated cytotoxicity and that the excess IL-4 production by SzS PBMCs was inhibited *in vitro* by IFN-γ. The Examiner also suggests that it would have been obvious to design a method of treating advanced cutaneous T cell lymphoma by administering recombinant IL-12 with an adjunct therapeutic agent which stimulates IFN-γ production because Haku et al. teach that recombinant IL-12 together with recombinant IL-2 at a suboptimal or optimal concentration augmented IFN-γ production and Rook et al. teach that augmenting IFN-γ production favors the enhancement of anti-tumor mediated immune responses. Finally the Examiner suggests that one would have been motivated to design a method for treatment of advanced cutaneous T cell lymphoma in a human by administering to said human IL-12 and an adjunct therapeutic agent which stimulates IFN-γ production, because this is a debilitating disease characterized by decreased IL-12, IL-2 and IFN-γ, and restoring normal levels of these cytokines would be expected to be beneficial to patients suffering from this disease.

Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

The cited combination of prior art references fails to meet all of these criteria with respect to the instant claimed invention.

Claims of the instant application are drawn to methods and compositions for treatment of advanced cutaneous T cell lymphoma in a human. Neither of the cited prior art methods provide one of skill in the art with a reasonable expectation of successfully treating advanced cutaneous T cell lymphoma in a human via administration of IL-12 alone or in combination with an adjunct therapeutic agent which stimulates interferon-γ production.

Instead, as acknowledged by the Examiner, Rook et al. (1996) describe *in vitro* culture experiments with PBMCs and the single cytokine IL-12. As discussed in detail in the instant application at pages 5 and 6, however, cytokine pathways are extremely complex

and exhibit cross-regulation, where the cytokines secreted by one subset of Th cells can block production and activity of cytokines secreted by the other subset. Accordingly, the success of administration of a single cytokine to a patient suffering from advanced cutaneous T cell lymphoma can not reasonably be predicted based upon *in vitro* experiments such as described by Rook et al.

Haku et al. also describe *in vitro* experiments in MNCs isolated from cancer patients. Further, as discussed in Section I, *supra*, this paper actually reports conflicting effects for IL-12 based upon the dose of IL-2 administered. Thus, this paper also fails to provide any reasonable expectation of successful treatment of advanced cutaneous T cell lymphoma in patients via administration of IL-12 alone or in combination with an adjunct therapeutic agent which stimulates interferon-γ production.

MPEP § 2143 and the Courts are quite clear; both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited combination of prior art fails to provide this reasonable expectation of success. It is only with the instant specification in hand, which demonstrates

efficacy of IL-12 administration in clinical trials (see pages 6-8), that one of skill has a reasonable expectation of success.

Accordingly, this combination of cited prior art does not render the instant claimed invention *prima facie* obvious. Withdrawal of this rejection under 35 U.S.C. § 103 is therefore respectfully requested.

III. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Kathleen A. Tyrrell
Registration No. 38,350

Date: **December 22, 2000**

LICATA & TYRRELL P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515